# Rising incidence of intrahepatic cholangiocarcinoma in the United States: a true increase?

Yasser H. Shaib[1,2,3], Jessica A. Davila[1,3], Kathryn McGlynn[4], Hashem B. El-Serag[1,2,3,*]

[1]Section of Health Services Research, The Houston Veterans Affairs Medical Center, Houston, TX, USA
[2]Section of Gastroenterology, The Houston Veterans Affairs Medical Center, Houston, TX, USA
[3]Baylor College of Medicine, Houston, TX, USA
[4]The National Cancer Institute, NIH, Bethesda, MD, USA

*Background/Aims*: The incidence of intrahepatic cholangiocarcinoma (ICC) has been reported to be increasing in the USA. The aim of this study is to examine whether this is a true increase or a reflection of improved detection or reclassification.

*Methods*: Using data from the Surveillance Epidemiology and End Results (SEER) program, incidence rates for ICC between 1975 and 1999 were calculated. We also calculated the proportions of cases with each tumor stage, microscopically confirmed cases, and the survival rates.

*Results*: A total of 2864 patients with ICC were identified. The incidence of ICC increased by 165% during the study period. Most of this increase occurred after 1985. There were no significant changes in the proportion of patients with unstaged cancer, localized cancer, microscopic confirmation, or with tumor size <5 cm during the period of the most significant increase. The 1-year survival rate increased significantly from 15.8% in 1975–1979 to 26.3% in 1995–1999, while 5-year survival rate remained essentially the same (2.6 vs. 3.5%).

*Conclusions*: The incidence of ICC continues to rise in the USA. The stable proportions over time of patients with early stage disease, unstaged disease, tumor size <5 cm, and microscopic confirmation suggest a true increase of ICC.
© 2003 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

*Keywords*: Intrahepatic cholangiocarcinoma; SEER; Incidence

## 1. Introduction

The incidence and mortality of intrahepatic cholangiocarcinoma (ICC) has been reported to be increasing worldwide [1–3]. Data from the WHO database indicate a global increase in ICC related mortality [1,2] in countries in Asia, Europe, America and Australia. For example, an increase in ICC-related mortality has been noted in England and Wales [3], and increasing incidence of ICC was also reported in Crete and Japan [4,5].

In the USA, approximately 17 300 new cases of primary liver cancer are diagnosed every year [6]. Data from the NCI's Surveillance, Epidemiology and End Results (SEER) indicate that approximately 10% of these are cases of ICC, and the rest are hepatocellular carcinoma. Using data from nine SEER registries, Patel reported an increase in the age-adjusted incidence of ICC in the USA from 0.13 per 100 000 in 1973 to 0.67 per 100 000 in 1997 [7]. However, it remains unclear whether this was a true increase or a reflection of increased detection and diagnosis of ICC.

Increased detection of cancer is usually associated with an increase in the proportion of patients with early stage cancers, small-size tumors and possibly improved short-term survival. Another possibility is that the increase in ICC incidence is a reflection of increased use of improved diagnostic tests (e.g. ERCP) leading to increased detection or reclassification of hepatobiliary tumors from what would have been previously described as unclassified, extra-hepatic cholangiocarcinoma, or hepatocellular carcinoma. However, if the rising incidence rates of ICC were due to increased detection in the absence of a true increase, they should plateau once the dissemination of testing has been achieved. The possibility of reclassification would be supported by an increase in the proportion of tumors with a confirmed tissue diagnosis. Lastly, the increasing incidence of ICC could be a reflection of increasing

prevalence of primary sclerosing cholangitis (PSC), a known risk factor for cholangiocarcinoma. PSC-related ICC is known to occur at a relatively early age with most studies reporting the peak incidence in the fifth decade [8]. Hence, if PSC is causing the observed increase in ICC incidence, we should expect a shift towards a younger age at diagnosis.

We conducted this study to examine whether these alternative hypotheses could explain the increase in ICC, and to update the incidence and survival trends of ICC in the USA.

## 2. Methods

### 2.1. Data source

Surveillance, Epidemiology, and End Results (SEER) Registries: Data for this study were obtained from SEER-Stat public use data files available on CD-ROM from the National Cancer Institute [10]. Beginning in 1973, the SEER registry program was established to identify all new cancer cases diagnosed within seven geographic areas, and by 1975, it included a total of nine geographic regions: five states (Connecticut, Hawaii, Iowa, New Mexico, and Utah) and four metropolitan areas (San Francisco-Oakland, Seattle-Puget Sound, Detroit-Metropolitan, and Atlanta-Metropolitan). In 1992, two additional registries were added to the program; these are the Los Angeles and San Jose registries. Overall, the SEER population is similar to the general USA population, particularly in regard to measures of poverty and education. However, SEER regions are more urban and have a higher proportion of foreign-born persons compared to the general USA population.

Demographic and cancer-related information included in this database are obtained from review of medical records. To evaluate the quality and completeness of these data, studies are conducted annually at each SEER registry to verify that data is being collected accurately, and that case ascertainment is at least 98% or greater. Cancers are coded according to the International Classification of Disease (ICD-O) [11].

### 2.2. Study population

All individuals identified from all SEER registries with a diagnosis of ICC between 1975 and 1999 were eligible for inclusion in this study. We included only cases with ICC (defined as cancer of the liver and intrahepatic bile duct and histology codes 8160, 8162, 8260, 8481, 8500 and 8560).

### 2.3. Statistical analyses

We calculated yearly incidence rates from all 11 registries for the 1992–1999 periods. Most of the analysis, however, was performed using the 1975–1999 data that are available only from nine registries. Because of the low yearly incidence rates of ICC, cohorts of patients with ICC were analyzed in five-yearly intervals (1975–1979), (1980–1984), (1985–1989), (1990–1994) and (1995–1999). For each of these cohorts, we calculated the age-adjusted and age-specific incidence rates of ICC. The incidence rates were calculated for the total number of cases as well as for different subgroups based on gender (men, women) and ethnicity (white, black, others). Incidence rate were reported with 95% CI. The incidence and mortality rates were adjusted against the age distribution of the USA population in 2000.

For all 5-year cohorts, we calculated the proportion of patients with a confirmed microscopic diagnosis defined by positive histology or a positive cytology. We also calculated the proportion of cases by cancer stage (localized, regional, distant, and unstaged) in all 5-year intervals. Previous studies have reported that the incidence of ICC started to increase after 1985 [7]; therefore, we examined the secular trends in the proportion of patients with microscopic confirmation and with staged disease throughout the study period as well as in a separate analysis restricted to the period after

1985. These trends were tested using the Cochran-Armitage trend test with $P$ values $< 0.05$ representing a significant trend.

Starting in 1988, tumor size was recorded in the SEER registry. Tumor size was obtained from pathology reports, operative reports or radiology reports (in this priority order) and reported as size in centimeters. We classified tumors into two size categories ($< 5$ or $\geq 5$ cm) and compared the proportion of patients in each size category in the last two intervals of the study period.

We calculated the observed, and relative survival rates at monthly intervals for 5 years following ICC diagnosis. The observed survival rate was calculated using standard life table procedures and represents the proportion of patients surviving for a specified length of time after cancer diagnosis. The expected survival rate is based on the mortality rate for the total population after taking into consideration age, sex, ethnicity and calendar year of diagnosis of the patients. The relative survival rate is calculated by adjusting the observed survival for expected mortality for a cancer-free cohort using a procedure described by Ederer et al. [9]. Relative survival is the best surrogate measure for cancer related mortality, which is often difficult to obtain.

All calculations were performed using the SEER*Stat version 4.2, the statistical package created for the analysis of the SEER database.

## 3. Results

Between 1992 and 1999, 2148 patients with ICC were identified in 11 SEER registries. The age-adjusted incidence rates of ICC increased by almost 20% from 0.75 per 100 000 (95% CI 0.65–0.85) in 1992 to 0.88 per 100 000 (95% CI 0.78–0.99) in 1999. However, because our primary aim is to examine temporal trends, all of the following analyses will pertain to 2864 patients with ICC were recorded in the original nine SEER registries between 1975 and 1999. Of these patients 54% were men and 46% were women. Classified by race 83% were white, 6% were blacks and the remainder (11%) was of other racial backgrounds predominantly Asians (Chinese, Japanese and Filipino). Approximately, 7% of ICC cases ($n = 209$) were classified as Klatskin tumors.

Using data from the original nine registries of SEER, there was a progressive increase in the age-adjusted incidence of ICC in the USA (Fig. 1). The age-adjusted incidence rates of ICC increased by 165% from 0.32 per 100 000 (95% CI 0.28–0.36) in 1975–1979 to 0.85 per 100 000 (95% CI 0.80–0.90) in 1995–1999. Most of this increase occurred during the second half of the study (after 1985). For example, the age-adjusted incidence of ICC increased 80% between 1985–1989 and 1995–1999 and 45% between 1975–1979 and 1980–1984. In general, men had higher age-adjusted incidence rates than women across all time intervals, but the temporal increase in incidence was similar in both groups. For example, between 1975–1979 and 1995–1999 the age-adjusted incidence rates for men increased from 0.40 per 100 000 (95% CI 0.33–0.47) to 1.06 per 100 000 (95% CI 0.97–1.16), and for women increased from 0.27 per 100 000 (95% CI 0.22–0.32) to 0.69 per 100 000 (95% CI 0.63–0.75). Among different racial groups (Fig. 2), whites and blacks had similar age-adjusted incidence rates while the rate among others (who are predominantly Asians) was approximately twice as high. For example, during 1995–1999, the age-adjusted
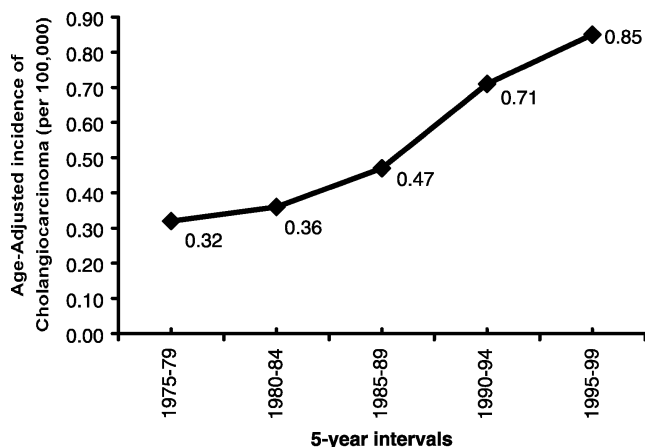
Fig. 1. The temporal trend of the overall age-adjusted incidence rates of intrahepatic cholangiocarcinoma in the USA between 1975 and 1999 shown in five 5-year intervals.

incidence of ICC was 0.83 per 100 000 (95% CI 0.77–0.89) among whites, 0.56 per 100 000 (95% CI 0.42–0.75) among blacks and 1.33 per 100 000 (95% CI 1.11–1.59) among others. Whites were the only group to maintain a progressive increase in the age-adjusted incidence of ICC while the age-adjusted incidence rates remained constant in blacks and others over the two most recent time intervals (1990–1994 and 1995–1999; Fig. 2).

The age-specific incidence of ICC increased across all age groups during the study period with the most significant increase noted among the older age groups (Fig. 3). This incidence doubled for people between 45 and 64 years of age (from 0.46 per 100 000 (95% CI 0.37–056) in 1975–1979 to 0.94 per 100 000 (95% CI 0.82–1.06) in 1995–1999) and tripled for people over 65 years of age (from 1.57 per 100 000 (95% CI 1.33–1.84) in 1975–1979 to 4.77 per 100 000 (95% CI 4.45–5.15) in 1995–1999). There was a significant interaction between age and ethnicity. Among people over 65 years of age, Asians had



Fig. 3. The temporal trends of the age-specific incidence rates of intrahepatic cholangiocarcinoma shown in successive five 5-year intervals between 1975 and 1995.

a five-fold increase of ICC incidence (from 1.35 per 100 000 in 1975–1979 to 7.88 per 100 000 in 1995–1999) compared to a three-fold increase among older whites (from 1.61 per 100 000 (95% CI 1.36–1.90) in 1975–1979 to 4.6 per 100 000 (95% CI 4.32–5.08) in 1995–1999) and blacks (from 1.13 per 100 000 (95% CI 0.44–2.65) in 1975–1979 to 3.53 per 100 000 (95% CI 2.46–4.92) in 1995–1999); data not shown.

The proportion of patients with unstaged ICC decreased from 36.2 to 16.3% between 1975–1979 and 1995–1999 ($P < 0.0001$; Fig. 4). However, during the periods of most significant increase in incidence (1985–1999), there were no significant changes in the proportion of patients with unstaged ICC ($P = 0.29$). Although the proportion of patients with early stage disease (localized) increased slightly from 17.4% in 1975–1979 to 22.3% in 1995–1999 (Fig. 4), this increase was not statistically significant ($P = 0.11$).

Examining the temporal change in the proportion of patients with microscopic confirmation shows that the proportion of patients who had microscopic confirmation of ICC diagnosis decreased over time. It decreased from 92%
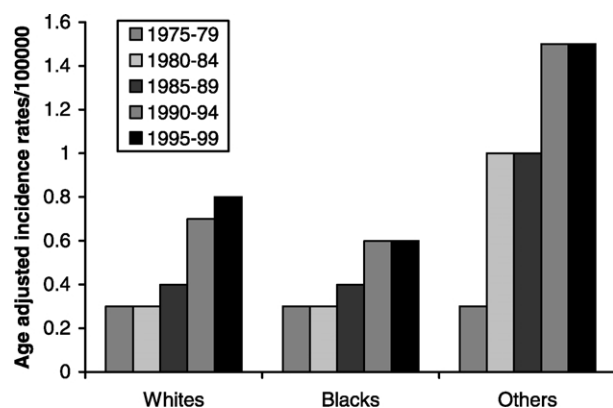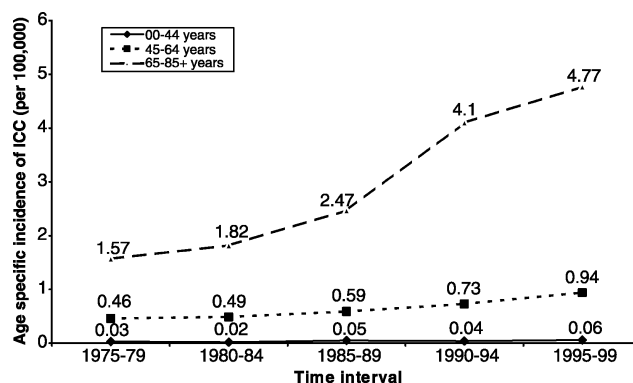


Fig. 2. The temporal trends of the age-adjusted incidence rates of intrahepatic cholangiocarcinoma among different ethnic groups shown in five 5-year intervals between 1975 and 1995.
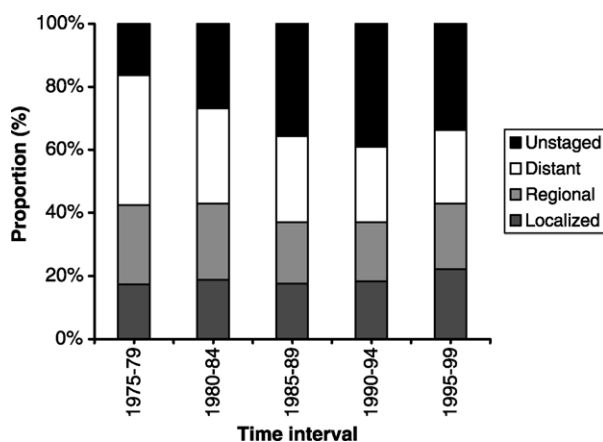


Fig. 4. The proportion of patients with different disease stages shown in successive 5-year cohorts between 1975 and 1999.
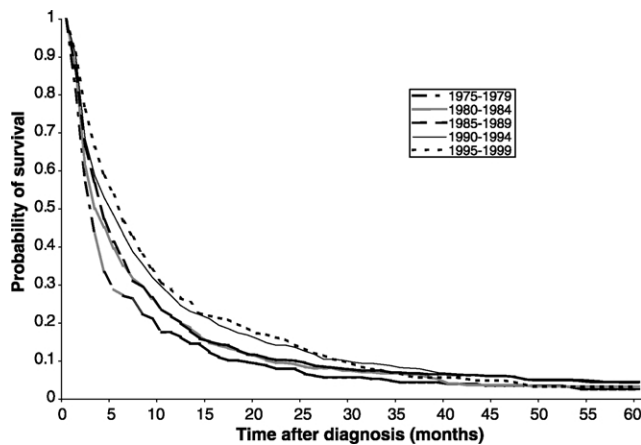
Fig. 5. The temporal trends of the relative survival rates of patients with intrahepatic cholangiocarcinoma following the diagnosis. The curves represent survival in successive 5-year cohorts diagnosed between 1975 and 1999. The top curve represents 1995–1999 while the bottom curve represents 1975–1979.

in 1975–1979 to 69% in 1995–1999. However, the trend of microscopic confirmation of ICC over the period of most sharp increase in ICC incidence (1985–1999) did not reveal any significant change ($P = 0.48$). The proportion of microscopically confirmed cases was 69% in 1985–1989 and 69% in 1995–1999.

Examining the tumor size over the last two intervals of the study period showed that the proportion of cases with tumors < 5 cm increased slightly from 23.4% in 1990–1994 to 25.4% in 1995–1999, but this increase was not statistically significant ($P = 0.32$).

The overall observed and relative survival of patients with ICC remained low with 75% of patients dying within 1 year of diagnosis for the entire study period (Fig. 5).

The 1-year relative survival, however, increased overtime from 16.4% (95% CI 6.4–26.4) in 1975–1979 to 27.6% (95% CI 20.1–34.4) in 1995–1999. This improved 1-year relative survival was noted among men and women in all ethnic groups and occurred mainly after 1989. On the other hand, the 5-year survival did not show any significant change and remained below 5% among all subgroups throughout the study period as well as during 1985–1999 (Table 1). For example, the 5-year survival of patients with ICC was 2.6% (95% CI 2.0–7.3) in 1975–1979, 3.4% (95% CI 1.5–8.3) in 1980–1984 and 3.5% (95% CI 2.6–9.5) in 1995–1999.

## 4. Discussion

This population-based study shows a persistent increase in the incidence of ICC in the USA between 1975 and 1999. It confirms and expands the previous findings reported by Patel (1975–1997) in the same nine SEER registries. It also demonstrates the same findings in a larger sample from 11 SEER registries between 1992 and 1999. In addition, the finding of stable proportions over time of early stage disease, unstaged disease and tumor size and microscopic confirmation indicate that most of the observed increase in ICC is likely to be a true phenomenon rather than a reflection of improved diagnosis or increased detection. The increasing overall incidence of ICC in the USA became apparent after 1985. Although the highest incidence rates were found among persons of non-white, non-black ethnic backgrounds (mostly Asians), the increase in incidence has affected men and women of all racial groups. However,

Table 1

The temporal trends in survival of patients with intrahepatic cholangiocarcinoma identified in the SEER registry between 1975 and 1999 (shown for successive 5-year cohorts with 95% CI)

| | 1975–1979 | 1980–1984 | 1985–1989 | 1990–1994 | 1995–1999 |
|---|---|---|---|---|---|
| *All cases* | | | | | |
| 1-year (%) | 16.4 (6.4–26.4) | 20.2 (10.4–29.9) | 20.1 (11.8–28.4) | 25.1 (17.7–31.7) | 27.6 (20.1–34.4) |
| 5-year (%) | 2.6 (2.0–7.3) | 3.4 (1.5–8.3) | 4.5 (0.20–9.2) | 4.2 (0.5–7.9) | 3.5 (2.6–9.5) |
| *Men* | | | | | |
| 1-year (%) | 9.7 (1.4–2.1) | 22.1 (9.1–35.0) | 19.3 (7.6–30) | 25 (15.6–34.8) | 28.6 (19.2–38.0) |
| 5-year (%) | 1.1 (0–5.3) | 5.1 (0–12.9) | 2.6 (0–7.7) | 4.8 (−0.5–10.1) | 3.9 (0–12.2) |
| *Women* | | | | | |
| 1-year (%) | 23.2 (6.9–49.8) | 16.8 (2.8–31.4) | 21.1 (9.1–33.3) | 24.2 (13.8–34.2) | 26.8 (17.2–36.1) |
| 5-year (%) | 4.1 (0–12.4) | 1.0 (0–5.2) | 6.5 (0–14.5) | 3.6 (0–8.6) | 0 |
| *Whites* | | | | | |
| 1-year (%) | 16.6 (5.8–27.4) | 21.1 (10.2–32.0) | 20.9 (1.6–30.1) | 25.0 (16.8–32.5) | 27.7 (20.3–35.1) |
| 5-year (%) | 3.0 (2.3–8.4) | 3.6 (0–9.1) | 4.7 (0–10.0) | 4.8 (0.4–9.2) | 0 |
| *Blacks* | | | | | |
| 1-year (%) | 8.6 (0–41.7) | 22.1 (0–60.0) | 7.3 (0–27.4) | 14.8 (0–37.0) | 21.3 (0–47.8) |
| 5-year (%) | 0 | 5.6 (0–29.4) | 0 | 2.7 (0–14.7) | 0 |
| *Others* | | | | | |
| 1-year (%) | 19.1 (0–58.7) | 11.2 (0–35.2) | 22.3 (0–49.6) | 28.8 (9.7–49.0) | 29.9 (11.7–47.8) |
| 5-year (%) | 0 | 0 | 4.8 (−0–23.2) | 1.4 (0–7.2) | 1.7 (0–10.4) |

during the 1990s only whites had a progressive increase in incidence rates.

An important finding in our study was that the proportion of patients with unstaged disease did not increase during the period of the observed increase in ICC incidence. Moreover, among patients with staged ICC, the proportion of patients with localized disease also did not increase over time. Lastly, there appears to be no significant change overtime in the size of ICC at the time of diagnosis. These findings argue against early detection as a significant explanation for the noted increase in incidence of ICC. Early detection would be expected to lead to improved staging, increased early stage cancers and smaller size tumors. Similarly, the degree of microscopic confirmation did not change during the time of the observed increase in ICC. This argues against reclassification from other tumors, e.g. hepatocellular carcinoma as a potential explanation for the increasing incidence of ICC.

The overall prognosis of ICC patients as indicated by survival remains poor. There was an improvement in the short-term survival (1-year survival) overtime, but not in the 5-year survival. Although we have not conducted a multivariate analysis to examine the concomitant effects of demographics and tumor features on survival, there were similar temporal trends in short- and long-term survival in all gender and ethnic groups. The improved short-term but not long-term survival can be attributed to improved palliative treatments (stenting and drainage) and/or improved overall supportive medical care. Alternatively the improved short-term survival could indicate lead-time bias related to early detection.

The reasons for the increase in ICC are not known. There had been a reported increase of PSC cases in the USA [12]. If the noted increase in ICC were to be attributed to PSC, one would expect a change towards a younger age at diagnosis because PSC-related ICC is diagnosed in at a relatively young age (47 years in one study [8]). Our study shows that the increasing incidence of ICC was not associated with a shift towards a younger age at diagnosis, with most patients diagnosed after 70 years of age and most of the increase occurring among people over 65 years of age. Other risk factors for ICC such as parasitic fluke infestations (e.g. Clonorchis sinesis) might have affected recent immigrants from Southeast Asia, but are unlikely to affect the general population. Therefore, they cannot explain the increasing incidence of ICC among whites who constituted the majority of ICC patients in the USA.

Hepatitis B virus (HBV) and hepatitis C (HCV) infections as well as liver cirrhosis independent of etiology have all been suggested as potential risk factors for cholangiocarcinoma [13–16]. At least three studies have examined the role of HCV and HBV infections in cholangiocarcinoma. A case-control study from Korea reported that subjects with ICC were more likely to be anti-HCV positive (odds ratio of 3.9), but not HBsAg positive (odds ratio of 1.3) when compared with controls [14]. Another study from Japan showed a relatively high incidence rate of ICC (2.3% over an average of 7.2 years) among 600 patients with HCV-related cirrhosis [15]. Similarly, a third case-control study from Italy reported an adjusted odds ratios of 9.7 and 2.7 for anti-HCV and HBs Ag positivity, respectively, among ICC case when compared to controls [16]. Yet many of the ICC patients in this study (39%) had liver cirrhosis. No studies of ICC and viral infections have yet been conducted in the USA.

In conclusion, our findings suggest that there has been a true increase in the incidence of ICC in the USA. The factors causing this increase are not clear. Large controlled studies are needed to examine potential risk factors underlying this increase.

# References

[1] Khan SA, Taylor-Robinson SD, Toledano MB, Beck A, Elliott P, Thomas HC. Changing international trends in mortality rates for liver, biliary and pancreatic tumors. J Hepatol 2002;37:806–813.

[2] Patel T. Worldwide trends in mortality from biliary tract malignancies. BCM Cancer 2002;2:10.

[3] Taylor-Robinson SD, Toledano MB, Arora S, Keegan TJ, Hargreaves S, Beck A, et al. Increase in mortality rates from intrahepatic cholangiocarcinoma in England and Wales 1968–1998. Gut 2001;48: 816–820.

[4] Okuda K, Nakanuma Y, Miyazaki M. Cholangiocarcinoma: recent progress. Part 1: epidemiology and etiology. J Gastroenterol Hepatol 2002;17:1049–1055.

[5] Mouzas IA, Dimoulios P, Vlachonikolis IG, Skordilis P, Zoras O, Kouroumalis E. Increasing incidence of cholangiocarcinoma in Crete 1992–2000. Anticancer Res 2002;22:6337–6341.

[6] Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thum MJ. Cancer Statistics 2003. CA Cancer J Clin 2003;53:5–26.

[7] Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. Hepatology 2001;33: 1353–1357.

[8] Chalasani N, Baluyut A, Ismail A, Zaman A, Sood G, Ghalib R, et al. Cholangiocarcinoma in patients with primary sclerosing cholangitis: a multicenter case-control study. Hepatology 2000;31:7–11.

[9] Ederer F, Axtell LM, Cutler SJ. The relative survival rate: a statistical methodology. Natl Cancer Inst Monogr 1961;6:101–121.

[10] Surveillance, Epidemiology, and End Results (SEER) program public-use CD-ROM (1973–1998). Bethesda, MD: National Cancer Institute; April 2001 (software).

[11] Percy C, Van-Holten V, Muir C, editors. International classification of diseases for oncology, 2nd ed. Geneva: World Health Organization; 1990.

[12] Wiesner RH, LaRusso NF. Clinicopathologic features of the syndrome of primary sclerosing cholangitis. Gastroenterology 1980; 79:200–206.

[13] Sorenson HT, Friis S, Olsen JH, Thulstrup AM, Mellemkjaer L, Linet M, et al. Risk of liver and other types of cancer in patients with cirrhosis: a nationwide cohort study in Denmark. Hepatology 1998; 28:921–928.

[14] Shin HR, Lee CU, Park HJ, Seol SY, Chung JMC, Choi HC, et al. Hepatitis B and C virus, Clonorchis sinesis for the risk of liver cancer: a case-control study in Pusan, Korea. Int J Epidemiol 1996;25: 933–940.

[15] Kobayashi M, Ikeda K, Saitoh S, Suzuki F, Tsubota A, Suzuki Y, et al. Incidence of primary cholangiocellular carcinoma of the liver in Japanese patients with hepatitis C virus related cirrhosis. Cancer 2000; 88:2471–2477.

[16] Donato F, Gelatti U, Tagger A, Facret M, Ribero ML, Callea F, et al. Intrahepatic cholangiocarcinoma and hepatitis C and B virus infection, alcohol intake, and hepatolethiasis: a case-control study in Italy. Cancer Causes Control 2001;12:959–996.